PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/052250	20.09.2004	19.09.2003

International Patent Classification (IPC) or both national classification and IPC
C12Q1/18

Applicant
TIBOTEC PHARMACEUTICALS LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-4,6,10,13,14 (partially), 20-24 (completely)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-4,6,10,13,14 (partially) are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 20-24 (completely)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7,12,15-19
	No:	Claims	1-6,8-11,13,14
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2004/052250

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: FENARD DAVID ET AL: 'Secreted phospholipases A2, a new class of HIV inhibitors that block virus entry into host cells' JOURNAL OF CLINICAL INVESTIGATION, NEW YORK, NY, US, vol. 104, no. 5, September 1999 (1999-09), pages 611-618, XP002178980 ISSN: 0021-9738

D2: OJWANG J O ET AL: 'T30177, AN OLIGONUCLEOTIDE STABILIZED BY AN INTRAMOLECULAR GUANOSINE OCTET, IS A POTENT INHIBITOR OF LABORATORY STRAINS AND CLINICAL ISOLATES OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1' ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, DC, US, vol. 39, no. 11, November 1995 (1995-11), pages 2426-2435, XP000946679 ISSN: 0066-4804

D3: PANNECOUQUE CHRISTOPHE ET AL: 'New class of HIV integrase inhibitors that block viral replication in cell culture' CURRENT BIOLOGY, vol. 12, no. 14, 23 July 2002 (2002-07-23), pages 1169-1177, XP002271109 ISSN: 0960-9822

D4: LIN PIN-FANG ET AL: 'A small molecule HIV-1 inhibitor that targets the HIV-1 envelope and inhibits CD4 receptor binding.' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. UNITED STATES 16 SEP 2003, vol. 100, no. 19, 16 September 2003 (2003-09-16), pages 11013-11018, XP002271110 ISSN: 0027-8424

D5: PAUWELS RUDI ET AL: 'Potent and selective inhibition of HIV-1 replication in vitro by a novel series of TIBO derivatives' NATURE, vol. 343, no. 6257, 1 February 1990 (1990-02-01), pages 470-474, XP002271145 ISSN: 0028-0836

D6: LEE AH ET AL: 'Generation of the replication-competent human immunodeficiency virus type 1 which expresses a jellyfish green fluorescent protein' BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ACADEMIC PRESS INC. ORLANDO, FL, US, vol. 233, no. 1, 7 April 1997 (1997-04-07), pages 288-292, XP002142659 ISSN: 0006-291X

D7: ANONYMOUS: 'Automation of Cell-Based Assays' INTERNET ARTICLE, [Online] April 2003 (2003-04), pages 1-4, XP002271114 Retrieved from the Internet: <URL:http://www.hudsoncontrol.com/files/ab 105b_cellassay_automation.pdf> [retrieved on 2004-02-20]

Re Item III.

1. The subject-matter of claims 1-4, 6, 10, 13, 14, 20-24 is not clear and/or supported by the description in the sense of Article 6 PCT.

1.1. There exists a large number of documents that are relevant to the issue of novelty regarding claims 1-4, 6, 10, 13, 14, because their subject-matter merely relates a classical time-of-addition assay for the screening of HIV inhibitors. D1-D5 represent some illustrative examples, but other documents might have to be taken into consideration in the future course of the examination procedure. Consequently, it was impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT) and the search was restricted to the subject-matter disclosed in claims 5, 7-9, 11, 12, 15-19.

1.2. Present claims 20-24 relate to compounds defined by reference to a desirable characteristic, namely "being identifiable with a claimed assay".

The claims cover all compounds having this characteristic, whereas the application provides no support at all within the meaning of Article 6 PCT and no disclosure within the meaning of Article 5 PCT for such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has not been carried out for those claims.

2. Present claim 24 relates to subject-matter not required to be searched by the International Searching Authority, namely Article 52(4) EPC, i.e. Method for treatment of the human body by therapy.

3. No examination of the claimed invention as to Novelty, Inventive Step and Industrial Application in respect of the (parts of the) claims mentioned above will be carried out.

Re Item V.

1. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-6,8-11,13-15 is not new in the sense of Article 33(2) PCT.

1.1. Concerning independent claim 1, the document D1 discloses (the references in parentheses applying to this document):

Multi-well assay for identifying a compound inhibiting the replication cycle of a micro-organism (figure 2a incl. legend) comprising the subsequent steps of preparing a multi-well comprising micro-organism coated host cells (legend to figure 2a: any time-of-addition assay implicitly requires the use and preparation of multiple assay wells, i.e. a "multi-well"); initiating at time t micro-organism infection and replication in said micro-organism-coated host cells such that micro-organism infection and replication is initiated synchronically in all host cells (legend to figure 2a: temperature shift from 4 °C to 37 °C); bringing at time t + Δt a candidate compound at one or more concentrations into contact with a part of the host cells (figure 2a: bvPLA2); repeating the previous step after a time interval of Δt for another part of said host cells (figure 2a: bvPLA2); optionally repeating the two previous steps using one or more other candidate compounds at one or more concentrations (figure 2a: AZT) determining whether said candidate compound has inhibited micro-organism replication in said host cells (legend to figure 2a: beta-gal assay).

1.2. Document D1 also discloses the subject matter of dependent claim 2 (legend to figure 2a: HIV-1), claim 3-5 (figure 2a as well as page 615, column 1, last paragraph to column 2, first line: the assay showed clearly different effects for the inhibitor of the "entry stage" bvPLA2 on one side and the inhibitor of the "reverse transcription stage" AZT on the other side), claim 8 (legend to figure 2a: temperature shift from 4 °C to 37 °C), claim 10 and 11 (legend to figure 2a and page 613, column 1, line 2-5: "P4 cells" are CD4+ cells in which transactivation by an HIV-protein induces expression of the LacZ gene from the HIV-1 long-terminal repeat) as well as claim 13 and 14 (legend to figure 2a: beta-gal assay; this implicitly requires the use of digital imaging techniques).

The subject-matter of claims 2-5, 8, 10, 11, 13, 14 is therefore not new (Article

33(2) PCT), either.

1.3. In addition, Document D2 discloses the subject matter of claim 6 (figure 5: 120 min) as well as claim 9 (page 2427, column 2, paragraph 4, line 1-5).

The subject-matter of claims 6 and 9 is therefore not new (Article 33(2) PCT), either.

1.4. Concerning independent claim 15, the document D7 discloses (the references in parentheses applying to this document):

Apparatus for carrying out a "time-of-addition" assay, comprising a support, vials, pipetting means and pipetting controlling means (these are the essential features of any liquid handler, e.g like the one of the cell-based assay workcell: last page, last paragraph) as well as environment controlling means (the hood enclosure of the cell-based assay workcell: last page, last paragraph).

The subject-matter of claim 15 is therefore not new (Article 33(2) PCT), either.

2. Dependent claims 7, 12, 16-19 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT with respect to inventive step (Article 33(3) PCT), because the features are known from document D1, D6 and D7 or are within the scope of the normal experience and competence of a skilled person.

3. Claims 1-19 appear to meet the requirements of the PCT with respect to the industrial applicability of their subject-matter (Article 33(4) PCT).